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Consumer goods
Pharmaceuticals

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REVIEW OF THE VARIATIONS REGULATIONS: OUTCOME OF THE PUBLIC CONSULTATION ('COMITOLOGY' PART)

This document summarises the contributions made by stakeholders to DG Enterprise and Industry's public consultation on variations conducted from 25 October 2007 to 4 January 2008. Stakeholders were invited to express their position on the basis of a draft Regulation and an accompanying Consultation Paper[1].

Contributors

The Commission received **47 contributions**. Many of them, in particular the ones from the industry, are the results of wider consultation. The participants can be divided into 3 categories: industry (association and individual companies), national authorities, and other stakeholders. A list detailing all contributors is provided in the Annex to this document.

All contributions received provided valuable information and comments for the Commission's further action in this field.

Summary of contributions

Generally speaking, all contributors welcomed the initiative taken by the Commission to make the framework on variations simpler, clearer and more flexible. Industry stakeholders, in particular, strongly emphasised the value of this project in terms of reduction of the administrative burden and optimisation of resources. The expectation from the vast majority of stakeholders is that the initiative will enable both industry and competent authorities to focus more on public/animal health issues and less on purely administrative matters.

Article 2 (Scope)

The principle of harmonised rules for changes to all types of medicines subject to a marketing authorisation, irrespective of their legal status and therefore including changes to 'purely national' marketing authorisations, was supported by the vast majority of stakeholders. The proposal was generally welcomed as *'a major step forward'*.

Some stakeholders requested clarification as to whether variations to Vaccine Antigen Master File and Plasma Master File should be included within the scope of this Regulation.

[1] http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

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Article 3 (Definitions)

The consultation showed that there is a mix of views as regards the definition of 'extensions' of marketing authorisations. Some stakeholders, in particular certain Member States competent authorities, considered that an extension is a change which cannot be handled *via* a variation procedure within one and the same marketing authorisation. According to these stakeholders, an extension leads to a new self-standing marketing authorisation, which is granted with its own marketing authorisation number additional to the already existing authorisation. On the other hand, other stakeholders considered that extensions should be classified as a subcategory of variations (as suggested in the draft subject to public consultation). This should however not prevent marketing authorisation holders from applying for additional strengths, pharmaceutical forms or route of administration (*i.e.* 'extension' types of changes) as a stand alone marketing authorisation application, under a separate name.

Some stakeholders also commented on the definitions of minor variations of Type IA and major variations of Type II and recommended alternative wordings to avoid the term "negative impact", which may lead to ambiguities.

Article 4 (Classification of variations):

The vast majority of stakeholders strongly welcomed the proposal to use the ' Type IB' category as the 'by default' classification category, while a minority considered that the current 'Type II by default' system should be kept. A number of contributors stressed the importance, under this new system, of a comprehensive and detailed list of major variations of Type II to be introduced in the detailed guidelines referred to in Article 6 (see below).This list should be as complete as possible and regularly updated, to minimise the risk that a major change is treated as a Type IB. The introduction of the 'switch/safeguard clause' (see below) was welcomed in this context, provided conditions triggering the use of this clause are clearly defined.

Some stakeholders also suggested that the Regulation should equally foresee the situation where the applicant may himself wish to submit an unclassified change as a Type II variation.

Article 5 (Scientific recommendation on unforeseen variations)

The proposal for advice on unclassified variations was generally welcomed as a mean to further harmonise interpretation of non-listed changes. While the majority of contributors considered that the task of delivering such advice could be given to the EMEA (as suggested in the draft), some raised concern over the workload that this new procedure would entail on the Agency. A role for the Coordination Groups for Mutual Recognition and Decentralised Procedures (CMD(h+v)) in the procedure was suggested, since the CMDs have extensive experience of processing variations for products authorised nationally and through mutual recognition/decentralised procedure. A system of questions and answers, to be agreed between the CMDs and the EMEA, was also proposed.

Article 6 (Guidelines)

The proposal to put the list of classification of variation in guidelines (instead of the current Annex I to the Variations Regulations) was strongly welcomed by nearly all contributors. This suggestion is deemed to bring important flexibility and adaptability to

the overall framework. Many stakeholders highlighted the importance of regular updates of this guideline, to accommodate the evolution of science and technology, as well as the need to involve all interested parties in the drafting process.

Some stakeholders proposed that the Annex III of the draft subject to public consultation (*i.e.* the documentation to be provided when submitting a variation) should also be put at guidance level. Conversely, others were of the view that it is appropriate to list the documentation to be submitted in the Regulation rather than in a guidance document, so as to maintain harmonisation and consistency in the requirements.

Finally, some stakeholders suggested that operational guidelines (*i.e.* guidelines necessary for the implementation of the Regulation) should not be drafted by the Commission but rather by the EMEA/CMDs.

Article 7 (Grouping of variations)

The notion of 'Do and Tell' and the proposed annual reporting system (*i.e.* grouping of Type IA notifications) were supported by the vast majority of Member States. Three issues, however, were raised:

i. What happens if the annual report reveals that invalid changes have been made in the past twelve months? In this respect, several contributors suggested to strictly limit the scope of the 'Do and Tell' procedure to changes that have no quality/safety/efficacy impact.

ii. How should the annual report be reviewed? A mix of views was expressed: some suggested a system where the authority does not systematically check every annual report but rather 'picks and chooses'. On the other hand other contributors clearly supported a systematic review.

iii. Should the annual reports be grouped per marketing authorisation holder for one given competent authority? The suggestion to allow for such grouping, as mentioned in the draft was rejected by a number of stakeholders. However, a majority seemed to support grouping of annual reports, provided the same package of minor variations would be applied to all concerned medicinal products (and not different packages for different products grouped together).

The grouping of Type IB/II/extensions was supported in principle, with the same question and emerging compromise as above (question (iii)). Some contributors, however, challenged the inclusion of extensions (see also Article 3).

Several stakeholders raised the issue of grouped variations which would be only partly acceptable (some variations in the group being acceptable, others being not). Should the system rely on a 'all or nothing' approval procedure, or should partial approval be allowed? A mix of views was expressed on this issue.

The combination of grouping and worksharing raised some comments. The majority of stakeholders considered that grouping could be combined with worksharing only if the group of variations is identical for all products concerned by the worksharing procedure. Others considered that grouping should not be combined with worksharing. A minority also suggested the possibility to allow worksharing even when the marketing

authorisations for the concerned medicinal products are owned by different marketing authorisation holders.

Articles 8-15 (Procedures for purely national marketing authorisations, mutual recognition and decentralised procedure)

This part of the draft raised mostly technical or editorial comments. It was understood that Articles 8 to 11 will be adopted only once the 'co-decision' legal base to the Variations Regulations has been modified to include variations to purely national marketing authorisations.

Article 16 (Arbitration, role of the CMDs)

Stakeholders supported this article in principle, but requested clarification on the role of CMDs in the context of arbitration procedures concerning variations, as well as on the grounds for disagreement.

A fixed timetable similar to what is currently laid down in Directives 2001/82/EC and 2001/83/EC (*e.g.* 60 days) for CMDs referrals was suggested. It was emphasised that centralised (EMEA/Commission) arbitration should only occur if no agreement has been reached at CMD level.

Many contributors also considered that the criteria for triggering a referral should be stricter. The existing criterion of “potential serious risk to public/animal health” was often raised as a model in this context.

Finally, a number of stakeholders considered that minor variations of Type IA should be excluded from the scope of the CMDs arbitration procedure. Some also proposed to restrict this procedure to major variations of Type II (*i.e.* excluding Type IB as well).

Article 17 (Type IA procedure, centralised)

This Article raised mostly comments of editorial or technical nature.

Article 18 (Type IB procedure, centralised; see also Articles 9 and 13)

The 'switch/safeguard' clause which enables authorities to switch from a Type IB to a Type II procedure raised several comments. A mix of views was expressed regarding the conditions for triggering this clause. Some stakeholders considered the conditions should be flexible, while others proposed to tighten them. A number of contributors also requested clarification on the timeline of the overall process; some suggested that the decision for Member States competent authorities to switch should be allowed only during the first 14 days of the Type IB procedure.

Articles 19-20 (Type II procedure and human influenza, centralised)

These Articles raised mostly comments of editorial or technical nature.

Article 21 (Closure of procedures)

The issue of the annual report (see Article 7 above) was also raised in this context. Some stakeholders suggested that if the variations notified through annual reporting do not

entail any amendments to the terms of the concerned marketing authorisations, then there should be no specific 'closure' procedure for these reports.

Other comments on this Article were of editorial or technical nature.

Article 22 (Implementation by economic operators)

This Article raised mostly comments of editorial or technical nature. Some stakeholders proposed to introduce a definition for the term 'economic operators'.

Article 23 (Extensions)

This Article triggered comments related to the legal definition of extensions, in relation to the definition of variations (see Article 3 above).

Article 24 (Worksharing)

The principle of worksharing was very much welcomed and supported by the vast majority of stakeholders. However, the following comments were made:

Most of the contributors from Member States national authorities rejected the proposal of a fully centralised EMEA-led evaluation system. The following compromise seemed to emerge from the contributions:

– Where at least one of the concerned products is authorised centrally, the EMEA should remain in charge of the evaluation.

– Where no centrally-authorised product is concerned, the authority in charge of the assessment would be chosen amongst the concerned Member States, by the marketing authorisation holder. Use of the CMDs to coordinate this worksharing procedure should be explored in this context.

On the other hand, the vast majority of contributors from the industry supported a fully centralised EMEA-led evaluation system.

A large number of stakeholders agreed with the need, following the evaluation of a 'workhsaring' variation, to introduce a fixed time period (*e.g.* 30 days) for competent authorities to accept (or reject) the outcome of the 'worksharing ' evaluation. Such a system should however take into account the arbitration mechanisms already in place in the case of products authorised under mutual recognition/decentralised procedure (see Article 16). It should also fully respect the right for national competent authorities, in the case of medicinal products authorised under the purely national procedure, to disagree with the outcome of the 'worksharing evaluation'.

Finally, several stakeholders questioned the scope of the worksharing procedure. Some suggested to restrict it to major variations (and possibly extensions). Others considered that Type IB variations should also be eligible.

Article 25 (Pandemic influenza)

Some stakeholders suggested that this specific procedure should also be applicable to all variations to pandemic influenza vaccines during an outbreak period, with the exception of minor variations of Type I and urgent safety restrictions.

Article 26 (Urgent safety restrictions)

This Article raised mostly comments of editorial or technical nature, to clarify its interpretation.

Annex I (Scope of extensions)

Several industry stakeholders suggested that some of the changes which are listed as extensions should be downgraded to Type II variations.

Other stakeholders proposed to modify this Annex in the case of 'simple' biotechnology-derived medicinal products, such as insulin, to provide for the possibility of an alternative manufacturing process within the terms of the same marketing authorisation.

Annex II (Scope of grouping)

Some stakeholders considered that the scope of grouping should be widened, for example by inserting a 'flexibility' clause that allows the applicant, if agreed by the concerned competent authority, to group variations which do not fall within one of the cases outlined in Annex II. On the other hand, other stakeholders highlighted that grouping should be restricted to cases where the changes are clearly related to each other.

Annex III (Documentation to be submitted)

See Article 6.

Annex: list of contributors to the public consultation

<u>Total:</u> 47 contributions

Industry (25 contributions):

Associations (15 contributions)

(1) ABPI – the Association of the British Pharmaceutical Industry (ABPI)

(2) AESGP – Association of the European Self-Medication Industry

(3) APIC – Active Pharmaceutical Ingredients Committee

(4) BPI – German Pharmaceutical Industry Association

(5) ECHAMP – European Coalition on Homeopathic and Anthroposophic Medicinal Products

(6) ECI – Eye-Care Industries European Economic Interest Grouping

(7) EFPIA – European Federation of Pharmaceutical Industries and Associations, including:

- EBE - European Biopharmaceutical Enterprises
- EVM - European Vaccines Manufacturers Association

(8) EGA – European Generic Medicines Association

(9) EGGVP – European Group for Generic Veterinary Products

(10) EuropaBio – European Association for Bioindustries

(11) IFAH-Europe – International Federation for Animal Health – Europe

(12) LAKIFA – Latvian Association of Chemical and Pharmaceutical Industry

(13) PAGB – Proprietary Association of Great Britain

(14) PHARMIG – Association of the Austrian pharmaceutical industry

(15) PhRMA - Pharmaceutical Research and Manufacturers of America

Individual companies (10 contributions)

(16) BMS – Bristol-Myers Squibb

(17) Doris Wangel, Flamel Technologies

(18) Grindex

(19) J&J – Johnson and Johnson

(20) MSD – Merck Sharp & Dohme (Europe) Inc., affiliate of Merck & Co., Inc.

(21) Novartis

(22) PCAS

(23) Teva – CMC Regulatory Group of the Global Innovative R&D Division

(24) West Pharmaceutical Services

(25) Wyeth

National authorities (18 contributions):

(26) AGES – Austrian Agency for Health and Food Safety

(27) AFMPS – Belgian Federal Agency for Medicines and HealthCare products

(28) BMG – German Federal Ministry of Health

(29) DKMA – Danish Medicines Agency

(30) NAM – Finnish National Agency for Medicines

(31) France

(32) Hungary – National Institute for Pharmaceuticals

(33) IMB – Irish Medicines Board

(34) IMCA – Icelandic Medicines Control Agency

(35) IT – Italian Regulatory Authority – Veterinary Medicinal Products

(36) LVVPI – Lithuanian State Inspection on Veterinary Preparations

(37) MEB – Dutch Medicines Evaluation Board

(38) NoMA – Norwegian Medicines Agency

(39) Poland – Office for Registration of Medicinal Products, Medical Devices and Biocides

(40) Portugal – INFARMED – Medicines Agency and DGV – Direcção Geral de Veterinária

(41) MPA – Swedish Medicines Products Agency

(42) SIDCO – Slovakian State Institute for Drug Control

(43) UK – MHRA Medicines and Healthcare Products Regulatory Agency and VMD – Veterinary Medicines Directorate

Other stakeholders (4 contributions):

(44) CMD(h) – Coordination Group for Mutual Recognition and Decentralised Procedures (human)

(45) EDQM – European Directorate for the Quality of Medicines, Council of Europe

(46) EMEA – European Medicines Agency

(47) (I)VMP – Dutch Assessors for veterinary medicinal products